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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,989	05/29/2001	Wilfred Wayne Lautt	2495.00071	7861

7590 07/24/2008

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,989	LAUTT, WILFRED WAYNE	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 19, and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114 received 4/30/08.

Applicant's statement regarding co-pending application 10/761,596 is acknowledged and made of record.

Status of the Claims\

Claims 1-3, 19, and 21-25 are currently pending in this application and are the subject of the Office action.

Claim Amendment

Applicant's following statements are acknowledged and made of record:

1) Claim 1 has been amended to further clarify the claimed subject matter; support for this amendment can be found at page 4, lines 26-27 of the specification.

2) Claims 21-25 are new; support for these claims can be found throughout the specification, including pages 12-14.

Response to applicant's arguments/remarks

Rejection under 103(a)

Applicant contends that this rejection should be withdrawn for essentially the following summarized reasons (see applicant's Response at pages 4-6):

1) The cited references relied upon by the examiner fail to support a prima facie case of obviousness.

2) Adams et al. postulates that ET antagonists could be used for ...

diabetics; however, this reference is concerned with peripheral vasoconstriction (col. 2, lines 24-31).

3) Adams et al. do not suggest a treatment for insulin resistance in Type II diabetes even though it suggests a treatment for diabetes related hypertension.

4) The cited references fail to suggest use of a NO donor in any other condition besides vasoconstriction/vasodilation. For example, the cited references fail to teach or suggest how NO donors by mediating endothelin expression would increase insulin sensitivity. Therefore, the examiner has failed to show a connection between NO donors and insulin sensitivity.

In response, this rejection is withdrawn in view of the claim amendment.

NEW REJECTIONS

NEW MATTER REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1-3, 19 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites the term "or at risk of developing Type II diabetes." Applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art. In fact, everyone is "at risk of developing Type II diabetes." With regard to claim 1, applicant has not shown the criticality of the limitation "at risk of developing Type II diabetes" in providing predictable operability of the invention to one of ordinary skill in

the art. Contrary to applicant's statement, the term "or is at risk of developing Type II diabetes" as recited in claim 1 is found not to be supported by the specification as originally filed (see specification, page 4, last para.):

> **The consequence of lack of HISS release is the absence of HISS results in severe insulin resistance. In this situation, the pancreas is required to secrete substantially larger amounts of insulin in order that the glucose in the blood is disposed of to prevent hyperglycemia from occurring. If this condition persists, insulin resistance will progress to a state of type 2 diabetes (non-insulin depend nt diabetes mellitus) and eventually will lead to a complete exhaustion of the pancreas thus requiring the patient to resort to**

Dependent claims 2, 3, and 19 are rejected for the same reason as these claims fail to correct the deficiency of the claim from which they depend (i.e. claim 1).

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the criticality in distinguishing patients who at risk of developing Type II diabetes from subjects who are not at risk of developing Type II diabetes.

Thus, claims 1-3 and 19 are rejected for introduction of new subject matter.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 19, and 21-25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30, 31, 32, 33, 34-39 of copending application 10/761,596. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would have been obvious in view of the referenced claims. The instant claims differ from the conflicting claims in that reference claim 30, for example, is directed to a kit comprising a) a first container comprising a unit dosage injectable formulation of a NO donor or NO agonist; and a second container comprising an oral dosage formulation of a NO donor or NO agonist; and reference claim 35, for example, is directed to a method of increasing insulin sensitivity comprising administering components “a” and “b” of the kit. In spite of the difference, someone of skill in the art would consider the instant claims to be an obvious variant of the claimed subject matter of the conflicting claims because it is obvious that drugs need to be package in containers.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending applications have not in fact been patented.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the term "wherein the kit comprises more than one tablet or capsule" which renders the claimed subject matter indefinite because claim 21 from which claim 25 depends does not provide proper support for the term "kit."

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, and 19 are rejected under 102(e) as being anticipated by Adams et al. (US Patent 6,165,975) as evidenced by Nagy et al. (US Patent 6,887,872).

The term "at risk of developing Type II diabetes" as recited in claim 1 is construed to encompass every subject, except Type I diabetic subjects.

Adams et al. (US Patent 6,165,975) teach a method of treatment, in an organism, of a vascular condition, comprising administration of at least one agent at a level which enhances NO and which does not appreciably alter normal systemic vascular tone in said organism, wherein the at least one agent is an NO donor selected from the group

consisting of glyceryl trinitrate, isosorbide 5-ononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine molsidomine (SIN-1) , S-nitroso-N-acetylpenicillamine (SNAP), S-nitrosoglutathione, and N-hydroxy-L-arginine (see abstract). Claim 1 recites “SIN-1, nitroprusside and SNAP.” Claim 3 recites “wherein said administering step comprises injecting the compound” which overlaps with the teaching of Adams et al. of injectable nitroprusside (column 1, line 66 to column 2, line 4). To the extent that the instant claimed method recite the step of administering the NO donor as the only active method step, the term *"wherein said insulin sensitivity is hepatic sensitizing substance (HISS) dependent insulin sensitivity”* as recited in claim 19 is considered to be an inherent underlined mechanism of action of NO donors as evidenced by the teaching of Nagy et al. (US Patent 6,887,872) that the HISS mechanism is sensitive to the blockage of nitrogen oxide synthesis and can be activated by exogenous NO-donors (col. 19, lines 59-62)

For these reasons, claims 1, 3, and 9 are found to be anticipated by the cited reference.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 19, and 21-25 are rejected under 103(a) as being unpatentable over Adams et al. (US Patent 6,165,975; already made of record), in view of Garfield (US Patent 5,698,738) and Lautt et al. (US Patent 5,561,165).

The term "at risk of developing Type II diabetes" as recited in claim 1 is construed to encompass every subject, except Type I diabetic subjects.

Adams et al. teach a method of treatment, in an organism, of a vascular condition, comprising administration of at least one agent at a level which enhances NO and which does not appreciably alter normal systemic vascular tone in said organism, wherein the at least one agent is an NO donor selected from the group consisting of glyceryl trinitrate, isosorbide 5-ononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, and N-hydroxy-L-arginine (see abstract). Instant claim 1 recites "3-morpholinosydnonimine molsidomine (SIN-1)," "nitroprusside," and "S-nitroso-N-acetyl-D, L-penicillamine (SNAP)," which are well known compounds that are clearly taught by the cited reference. Adams et al. also teach that NO, in humans and animals, produced via sodium nitroprusside (SNP) infusion, causes vasodilation in peripheral vasculature at doses greater than 10 micrograms/kg per minute (column 1, line 66 to column 2, line 4); SNP may be

administered in a convenient manner such as by injection (column 15, lines 35-37). The term *"administering to the patient an effective amount of a therapeutic nitric oxide donor compound"* as recited in claim 1, for example, given its broadest reasonable possible interpretation, is construed to be satisfied by the teaching of the cited reference of NO donors in amounts to enhance NO levels (see abstract). Claim 1 also recites the term *"in a mammalian patient."* Claim 2 recites the term *"wherein said administering step comprises orally administering the compound,"* which is reasonably construed to overlap with the teaching of Adams et al. that SNP may be administered in a convenient manner (col. 15, lines 35-37). Claim 3 recites the term "wherein said administering step comprises injecting the compound," which also overlaps with the teaching of Adams et al. of SNP infusion (col. 15, lines 35-37). Adams et al. teach that NO performs a function through interaction with endothelin (ET), and that ET is under inhibitory control of NO, such that administration of NOS inhibitors results in elevated levels of ET (column 2, lines 2-11). Adams et al. also disclose that a number of investigators have postulated that ET antagonists could be used for conditions including diabetes (column 2, lines 24-31). The term "increasing insulin sensitivity" as recited in claim 1 is deemed to be coextensive with administering a therapeutic NO compound. Adams et al. do not teach the limitation of hepatic sensitizing substance (HISS) dependent insulin sensitivity as recited in claim 19, or oral dosage forms, or unit dosage formulations.

Garfield et al. (US Patent 5,698,738) is added to show the general knowledge in the art regarding the connection among nitric oxide pathways, diabetes, and

hypertension (col. 1, line 11 to col. 5, line 17, including Table 1), as well as dosage formulations containing NO donors. Garfield et al. teach that there is a substantial body of evidence from animal experiments that a deficiency in nitric oxide contributes to the pathogenesis of a number of diseases, including hypertension, atherosclerosis and diabetes (col. 1, lines 56-68; see also col. 3, Table 1). Garfield et al. teach that inhibition of nitric oxide synthase dramatically increases blood pressure (col. 1, lines 61-62). Garfield et al. also teach parenteral and oral dosage forms, and unit dosage forms comprising NO donors (col. 9, lines 17-59). The limitations with respect to the routes of administration (e.g. orally, injection – claims 2,3,); unit dosage formulation (e.g. claim 21); formulation (e.g. tablet or capsule e.g. claim 24-25) are clearly taught by Garfield et al. (col. 9, lines 17-59). The sequence of administering steps “a” and “b” as recited in claim 21 is considered within the scope and skill of an artisan skilled in the art as Garfield et al, teach parenteral and oral dosage forms, and unit dosage forms, comprising NO donors (col. 9, lines 17-59). For purposes of this rejection, the term "wherein the kit comprises more than one tablet or capsule” as recited in claim 25 is considered to be satisfied by the teaching of tablet and capsule by Garfield et al. because tablet and capsule are routinely packaged for commercial use in containers comprising multiple doses of tablets and capsules (col. 9, lines 17-59).

Lautt et al. (US Patent 5,561,165) is added to show the general knowledge in the art regarding the connection between insulin sensitivity/insulin resistance, HISS, and diabetic neuropathies. Lautt et al. teach a method for increasing insulin responsiveness

and improving glucose tolerance in a mammal in which insulin responsiveness and glucose tolerance are impaired comprising administering an effective amount of a cholinergic agent (column 1, lines 35-40). Lautt et al. teach that non-insulin dependent diabetes mellitus (NIDDM) may show insulin resistance and impaired glucose tolerance, as well as parasympathetic neuropathies, and that patients with chronic liver disease also show insulin resistance (column 1, lines 9-14). The term *"wherein said insulin sensitivity is hepatic sensitizing substance (HISS) dependent insulin sensitivity"* as recited in claim 19 is reasonably construed to be coextensive with practicing the instant claimed method.

Based on the teaching of Garfield et al. of the advantage of non-carcinogenic NO donors with high stability, a person of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of the above cited references to create the instant claimed inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Relevant Art of Record

The below cited art references made of record and relied upon are considered pertinent to applicant's invention.

Nagy et al. (US Patent 6,887,872) teaches that the HISS mechanism is sensitive to the blockage of nitrogen oxide synthesis and can be activated by the exogenous NO-donors (col. 19, lines 59-62). Nagy et al. also disclose the following (see col. 20):

The compounds of the formula I have an effect on the insulin sensitivity, and they are able to alleviate insulin resistance through nitrergic mechanism and sensory neurotransmitters. The normalization of insulin sensitivity have causal role in diseases of high morbidity and mortality such as type II diabetes, hypertension, coronary heart disease, obesity and some endocrine diseases.

Lautt (US Patent Application Pub. No. 2004/0151785 A1) teach a method of increasing insulin sensitivity by administering an effective amount of a compound which stimulates nitric oxide production in the liver (abstract). Lautt discloses that like conditions such as chronic essential hypertension, obesity, and liver disease, non-insulin dependent diabetes mellitus (NIDDM) show insulin resistance, impaired glucose tolerance and parasympathetic neuropathies (para. 0002). Lautt teaches compounds and methods of increasing insulin sensitivity by administering an effective amount of a compound which stimulates nitric oxide in the liver; said methods are useful in treating obesity, insulin resistance, and other conditions associated with insulin resistance (para. 0028). Lautt also exemplify L-NMMA and L-NAME (see paras. 0018-0026).

Szilvassy et al. (US Patent Application Pub. No. 2004/0068005 A1) teach pharmaceutical combinations for treatment and/or prevention of all sorts, periods and complications of diabetes mellitus in mammals, including the pre-diabetic diseases and their complications, optionally including ischemic heart diseases comprising an effective dose of at least one enzymatic nitric oxide (NO) donor active ingredient (abstract). Preferred enzymatic donors include a nitroglycerin, isosorbide mononitrate, erythityl terranitrate, pentaerythritol-tetranitrate (abstract).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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15 July 2008

/C. R./

Examiner, Art Unit 1611

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/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615